FOR PHYSICIANS, NURSES, AND PHARMACISTS

State of The Art Management of POSTTRANSPLANT SEQUELAE

PRESENTED BY:

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES OF
THE NATIONAL INSTITUTES OF HEALTH
U S DEPARTMENT OF HEALTH AND HUMAN SERVICES

Impact and Management of Cardiovascular Risks After Kidney Transplantation

FIRST IN A SERIES OF MONOGRAPHS

BASED ON A ROUNDTABLE HELD JANUARY 28, 2005, IN BETHESDA, MARYLAND

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Financial Support

This program is supported by an unrestricted educational grant from Wyeth.

Educational Objectives

At the conclusion of this program, participants will be able to:

- Recognize the prevalence and long-term impact of overall cardiovascular disease, and specifically hypertension and dyslipidemias, in renal transplant recipients
- Describe the risk factors for hypertension and dyslipidemias
- Identify the effects of immunosuppressive drugs on the development of hypertension and dyslipidemias
- Outline the modifications to immunosuppressive regimens to help manage hypertension and dyslipidemias
- Discuss the interventions to treat hypertension and dyslipidemias

Target Audience

Transplant surgeons, transplant nephrologists, transplant nurses, transplant coordinators, pharmacists, and other healthcare professionals who are involved in the treatment and management of renal transplant recipients

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Faculty Disclosure Information

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Faculty Member	Grants/Research Support	Consultant	Speakers Bureau
J. J. Curtis, MD	No affiliation or financial interest		
O. Gaber, MD	Fujisawa Healthcare, Inc; Genzyme Corporation; Novartis; Roche Laboratories Inc; Wyeth-Ayerst Laboratories		Wyeth-Ayerst Laboratories
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R. H. Rubin, MD		Merck & Co, Inc; Merrimack; Pfizer Inc; Roche Laboratories Inc	
R. P. Winsett, PhD	No affiliation or financial interest		
E. S. Woodle, MD	Enzon, Inc; Fujisawa Healthcare, Inc; Genzyme Corporation; Roche Laboratories Inc; Wyeth-Ayerst Laboratories		

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Presented by

National Institute of Allergy and Infectious Diseases
National Institutes of Health
Division of Allergy, Immunology, and Transplantation
Bethesda, Maryland

Represented by

Shiv A. Prasad, PhD
Chief, Transplantation Immunobiology Branch
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Program Chair

Bertram L. Kasiske, MD
Professor of Medicine
University of Minnesota
Minneapolis, Minnesota

Faculty

John J. Curtis, MD
Professor of Transplant Nephrology
Professor of Surgery, Division of Transplantation
University of Alabama at Birmingham
Birmingham, Alabama

Osama Gaber, MD
Professor, Department of Surgery
Associate Professor, College of Nursing
University of Tennessee Health Science Center
Memphis, Tennessee

Robert H. Rubin, MD
Osborne Professor of Health Sciences and Technology
Professor of Medicine, Harvard Medical School
Associate Director, Division of Infectious Disease
Brigham and Women's Hospital
Director, Center for Experimental Pharmacology and Therapeutics,
Harvard University-Massachusetts Institute of Technology
Division of Health Sciences and Technology
Boston, Massachusetts

E. Steve Woodle, MD
Professor of Surgery
Director, Division of Transplantation
Chairman, Board of Directors
Israel Penn International Transplant Tumor Registry
Department of Surgery
University of Cincinnati College of Medicine
Cincinnati, Ohio

Rebecca P. Winsett, PhD
Associate Professor, College of Nursing
University of Tennessee Health Science Center
Memphis, Tennessee

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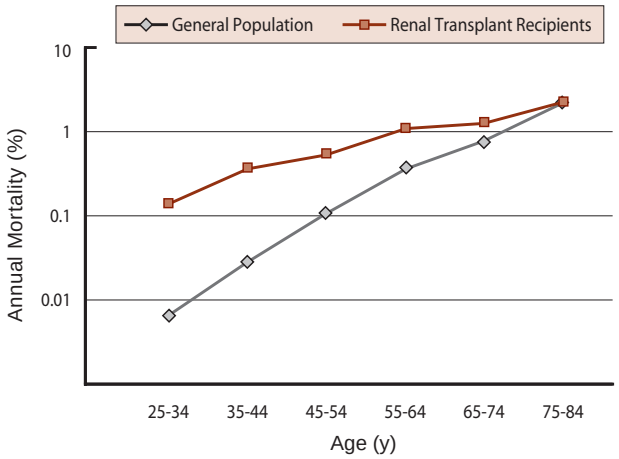
Introduction

Remarkable progress over the last decades due to advances in immunosuppressive therapies and transplantation technology has resulted in improved 1-year kidney graft survival, now exceeding 90%.[1] Although transplantation for patients with end-stage renal disease (ESRD) confers a survival advantage superior to that of maintenance dialysis,[2] longer-term morbidity and mortality for the transplant recipient are closely associated with development of cardiovascular disease. Currently, cardiovascular disease accounts for nearly 40% of deaths among renal transplant recipients (Figure 1), a rate that is considerably greater than that for the general population and more dramatic for younger than for older patients (Figure 2).[3,4]

Reviews of available evidence conclude that kidney transplant recipients have many of the same risk factors for cardiovascular disease as those traditionally found in the general population, such as risk factors recognized in the Framingham Heart Study (FHS)[5,6] and in the National Cholesterol Education Program (NCEP). However, additional cardiovascular disease risk factors have been identified for transplant recipients. Although an observational study found that the risk calculated from the FHS did predict ischemic events in kidney transplant recipients at more than 1 year posttransplantation, the risks were underestimated for the transplant population compared to the general population. Specifically, the increased risks among transplant recipients were associated with diabetes mellitus and, to a lesser degree, age and smoking.[5] Risk factors unique to transplant recipients that also may be more critical than the traditional risk factors include decreased renal function, development of proteinuria, and use of immunosuppressive medications.[7-10] Although lipid abnormalities and hypertension are common risk factors for both transplant recipients and the general population,[5] the very high incidence of these factors among kidney transplant recipients compels further investigation of their prevalence and potential causes, as well as identification of modifiable factors and therapeutic interventions. The National Kidney Foundation offers guidelines for the management of dyslipidemias and hypertension.[11-13]

Figure 2

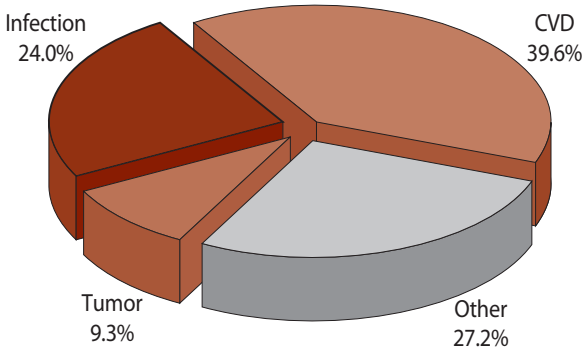
Annual Cardiovascular Mortality for Renal Transplant Recipients and the General Population by Age Group[3]



Adapted with permission from Foley RN, et al. *Am J Kidney Dis*. 1998;32:S112-S119.

Figure 1

Causes of Mortality in Renal Transplant Recipients[14]



USRDS 1st Kidney Transplants 1994-2000 (N=67,874)

USRDS = United States Renal Data System; CVD = cardiovascular disease.

Courtesy of Bertram L. Kasiske, MD

Hypertension

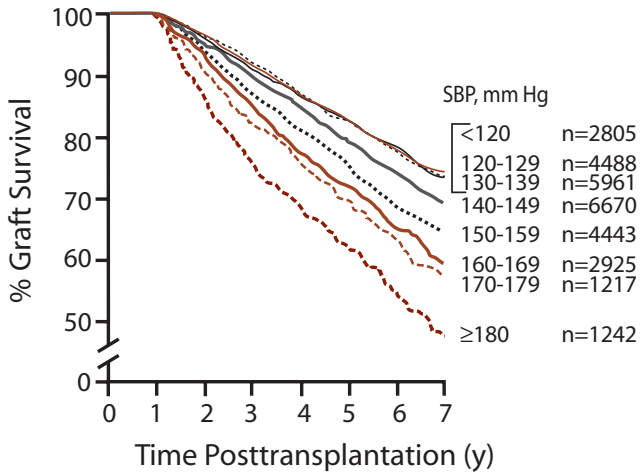
Estimates of the prevalence of hypertension and its relationship to outcomes

Hypertension in the kidney transplant recipient is extremely common, and, despite the variety of antihypertensive medications available, management of hypertension remains a challenge. A recent analysis portrays the situation now encountered in the transplant community with estimates of 87.6% of patients with blood pressure (BP) higher than normal (normal systolic BP defined as <120 mm Hg) and only 3.5% with truly normal BP in the absence of antihypertensive medication at 1 year posttransplantation.[15] Even this prevalence may be an underestimate since ambulatory BP monitoring of kidney transplant recipients revealed that office BP measurements fail to detect hypertension in 15% of patients considered normotensive.[16]

Hypertension is an independent risk factor for poorer long-term kidney graft survival in a variety of different studies.[15,17,18] Graft and patient survival rates analyzed over 7 years from data collected through the Collaborative Transplant Study international registry showed that increased levels of systolic and diastolic BP 1 year after transplantation were associated with gradual increases in risk of graft failure (P<.0001 at 7 years) (Figure 3).[17] A report from the United States further showed that each 10 mm Hg increase in systolic BP was associated with an increased risk of graft failure (P<.0001), death-censored graft failure (P<.0001), and death (P<.0001), independent of acute rejection and other transplant variables. Some of the relationship of BP to graft failure was evident at least 5 years prior to graft loss, but at 1 year posttransplantation 45.5% of patients had uncontrolled hypertension (systolic BP ≥140 mm Hg).[15]

Figure 3

Association of Systolic Blood Pressure (SBP) With Decreased Graft Survival[17]



Adapted with permission from Opelz G, et al. *Kidney Int*.1998;53:217-222.

Factors associated with posttransplant hypertension

Some causes of posttransplant hypertension include poor allograft function,[19] source of the donor kidney,[8] retention of the native diseased kidneys,[15,20] transplant renal artery stenosis,[21] and immunosuppressive drugs.

The origin of essential hypertension is a practical issue for the transplant community in deciding whether organs from hypertensive donors should be accepted or if more emphasis should be placed on other mechanisms of BP control.[22] Whereas some investigators believe that essential hypertension is not caused by the donor kidney but is more of a systemic disease that can recur,[8] the physiologist Guyton postulated that the kidney is the prime factor in hypertension.[23] The central role of the kidney was illustrated in a pivotal study of patients with essential hypertension who required kidney transplantation. The recipients remained normotensive for 4.5 years after receiving a kidney from a normotensive donor, with BPs not significantly different from those of the normotensive control subjects.[24] Overall, there is consensus that essential hypertension is kidney disease.

Use of some immunosuppressive drugs has become associated with subsequent hypertension. Corticosteroids are associated with only a 15% incidence of hypertension, and corticosteroid withdrawal does have a positive impact on BP control.[10,25] Paradoxically, although the introduction of calcineurin inhibitors (CNIs) benefited the transplant recipient with greatly increased graft survival, with their widespread use came an increased incidence of hypertension.[7] The first widely used CNI, cyclosporine, increases BP in solid organ transplant recipients with or without concomitant use of corticosteroids and in a dose-related manner. In a retrospective study, the use of cyclosporine for at least 1 year posttransplantation and the use of higher doses of prednisone were associated with higher BP.[15] Hypertension alleviation is possible if cyclosporine is discontinued early.[7] Since the CNI tacrolimus also produces hypertension,[10,26] the underlying intracellular mechanism believed responsible for both immunosuppressive activity and elevated BP is the inhibition of calcineurin.[27] In contrast, the immunosuppressive agent sirolimus does not appear to cause hypertension because it does not interact with calcineurin.[28]

In general, evidence suggests that of the CNIs, tacrolimus causes less hypertension than does cyclosporine.[28] Two prospective clinical trials in kidney transplantation compared the outcomes of patients randomized to receive either tacrolimus- or cyclosporine-based immunosuppression. The first report showed that after 6 months of follow-up in 557 patients, a significantly lower proportion of patients in the tacrolimus arm had hypertension than in the cyclosporine arm (15.7% vs 23.2%, respectively; P=.032).[29] In a separate study of 94 patients, the incidence of hypertension was similar in the two groups until the 3-year measurement, at which time a significantly higher percentage of patients were on antihypertensive medication in the cyclosporine group than in the tacrolimus group (74% vs 50%, respectively; P<.05).[26] The clinical comparison studies of hypertension caused by these two agents are difficult to interpret because if the hypertensive mechanism relies on calcineurin inhibition, the two CNIs should

have similar effects. However, if this is not the observed clinical effect, the question becomes whether CNIs cause hypertension through mechanisms that are independent of their effects on calcineurin.

A multicenter, randomized trial of tacrolimus in combination with either sirolimus or mycophenolate mofetil (MMF) evaluated short-term results at 6 months among 361 kidney transplant recipients. Although patient and graft survival and systolic BP were similar, diastolic BP was higher in the tacrolimus/sirolimus group than in the tacrolimus/MMF group (P=.02).[30]

A viable option for hypertension reduction is to institute early immunosuppressive agent withdrawal or minimization. In a long-term study of sirolimus after early cyclosporine withdrawal, 430 eligible recipients were randomized to remain on cyclosporine/sirolimus/corticosteroid maintenance immunosuppression or to undergo cyclosporine withdrawal with sirolimus/corticosteroid maintenance. After 2 years of follow-up, graft and patient survival and acute rejection rates were similar, but systolic BP was significantly lower in recipients who had only sirolimus/corticosteroid-based immunosuppression than in those continuing the cyclosporine regimen (134 mm Hg vs 141 mm Hg, respectively; P<.001).[31] In contrast, a large, randomized, multicenter European trial (N=833) instituted a controlled withdrawal of the two adjunctive agents, corticosteroids or MMF, from a tacrolimus-based regimen in renal transplant recipients; however, there was no significant difference in rates of patient or graft survival, acute rejection rates, or incidence of hypertension after 6 months.[32]

The goal in choosing an immunosuppressive regimen is, of course, to maintain the survival of the patient and graft while reducing long-term side effects. Hypertension is only one of the many potential side effects to consider in the choice of immunosuppressive drugs (Table 1).

Management of Hypertension

Although no clinical trials have prospectively investigated the degree of BP control and long-term outcomes in kidney transplantation, retrospective analyses have indicated that patients with lower BP have better overall survival and graft survival. So antihypertensive drugs are now routinely prescribed for hypertensive kidney transplant recipients, but management may complicated by the presence of diabetes or proteinuria from poor allograft function. Target BP levels in renal transplant recipients have been recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) and the European Best Practice Guidelines Expert Group on Renal Transplantation (Table 2).[33,34]

Table 1

Side Effect Profiles of Immunosuppressive Agents

	CsA	Tac	Srl	Ster	MMF
Hypertension	++	+	∅	++	∅
Hyperglycemia	+	++	∅	+++	∅
Renal insufficiency	++	++	∅	∅	∅
Hyperlipidemia	++	+	++	++	∅
Hyperkalemia	+++	+++	∅	∅	∅
Tremor	∅	+	∅	∅	∅
Hirsutism	+	∅	∅	∅	∅
Gingival hyperplasia	+	∅	∅	∅	∅
Hypophosphatemia	++	++	+	∅	∅
Osteoporosis	±	±	∅	+++	∅
Malignancy	+	+	?	∅	+

CsA = cyclosporine; Tac = tacrolimus; Srl = sirolimus; ster = steroids; MMF = mycophenolate mofetil; +++ = severe; ++ = moderate; + = mild; ± = opposite; ø = none; ? = unknown.

Adapted from Dr Martin Zand.

Diuretics

Although no comparative trials are available for evaluation of diuretics in posttransplant hypertension, there is general agreement that especially in transplant recipients with volume overload, diuretics are necessary for BP control.[1,10]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)

Initial reluctance to use ACE inhibitors after kidney transplantation was originally based on fears of hyperkalemia and abrupt declines in glomerular filtration rate (GFR) in patients with transplant renal artery stenosis.[1,10,35] However, more recent studies have reinforced the safety and effectiveness of these agents, which also now appear to have genuine application in hypertensive

Table 2

Blood Pressure Target Levels in Renal Transplant Recipients[33,34]

National Kidney Foundation (K/DOQI Guidelines)	<130/80 mm Hg
EBPG Expert Group on Renal Transplantation	
Without proteinuria	<130/85 mm Hg
With proteinuria	<125/75 mm Hg

K/DOQI = Kidney Disease Outcomes Quality Initiative; EBPG = European Best Practice Guidelines.

transplant recipients with left ventricular hypertrophy or chronic allograft nephropathy,[10] as well as use in the early posttransplant period (first 90 days).[36] ACE inhibitors are also effective in reducing both hematocrit and hemoglobin levels in those patients with posttransplant erythrocytosis.[1,37]

The ACE inhibitors and ARBs may help preserve renal function as well as lower BP.[38,39] In an early study of 22 kidney transplant recipients, treatment with enalapril reduced proteinuria without changing creatinine clearance.[40] Furthermore, a Canadian chart review showed that of 177 renal transplant recipients prescribed either an ACE inhibitor or an ARB, mean arterial pressure decreased at each measurement point and significantly from a mean of 92 mm Hg to 86 mm Hg over 3 years (P<.05) without a change in creatinine clearance.[37] Additional studies have shown renal benefits during treatment with losartan,[41] captopril,[41] and lisinopril.[42]

Calcium channel blockers (CCBs)

CCBs, particularly the dihydropyridine CCBs, are attractive antihypertensive agents in transplant recipients because they dilate the afferent arteriole, thus reversing CNI-related vasoconstriction that may lead to progressive renal function decline.[43] Among many trials conducted in renal transplantation, a multicenter, placebo-controlled study randomized 210 kidney transplant recipients to receive either the CCB isradipine or placebo. At both 3 and 12 months posttransplantation, renal function was significantly better in the treatment group than in the placebo group (P=.002 at 3 months and P=.021 at 12 months), without a negative impact on the incidence or severity of delayed graft function or acute rejections.[44] Other CCBs, including amlopidine,[45] nifedipine,[46] and felodopine,[47] have specifically shown benefits for graft functioning in transplant recipients. Therefore, a number of studies have confirmed that dihydropyridine CCBs are effective in improving renal blood flow and GFR.[1,43] Unfortunately, nondihydropyridine CCBs (eg, verapamil and diltiazem) interact with the cytochrome P450 (CYP) 3A4 isoenzyme, so coadministration with a CNI can lead to noteworthy pharmacokinetic and pharmacodynamic interactions.[1] Additionally, concerns expressed in the nontransplant literature over potential harm of dihydropyridine CCB use in patients with kidney disease[48] have led to cautionary use in transplantation.

ACE inhibitors versus CCBs

Currently, no single antihypertensive agent or class is recommended over another, but the impression is that most transplant programs use ACE inhibitors first. Studies have been conducted to evaluate any differential benefit of ACE inhibitors and CCBs. A prospective study randomized 154 renal transplant recipients with hypertension to receive lisinopril or controlled-release nifedipine. In this study, both agents achieved good BP control, but statistically significant increases in GFR from baseline values were observed only in the nifedipine group at 1 year (P<.0001). Serum creatinine levels were also significantly decreased in the nifedipine group compared to baseline at 1 year (P=.013) but not in the lisinopril group.[49] A recent large retrospective study evaluated the relationship between BP and antihypertensive use in 1662 renal transplant recipients. Among the antihypertensive drug classes evaluated, only CCBs were associated with a reduction in graft loss (relative risk [RR],0.81; 95% confidence interval [CI], 0.68-0.96; P=.0236), whereas only ACE inhibitors/ARBs were associated with significantly lowering urinary protein excretion (P=.041).[39] In summary, no single class of antihypertensive agent has been demonstrated to be superior in maintaining renal allograft function. However, the reality is that most kidney transplant recipients will eventually require agents from most antihypertensive classes for BP control.

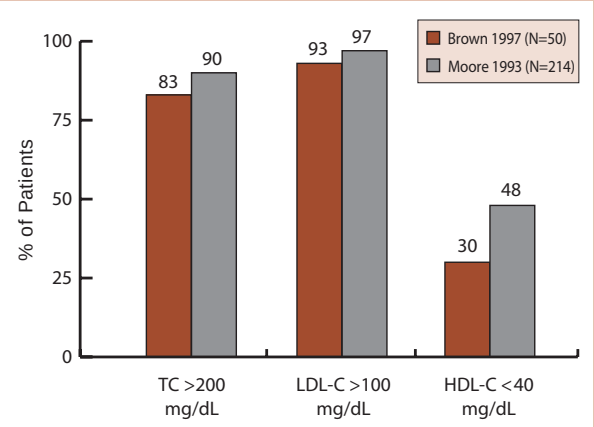
Dyslipidemias

The prevalence of dyslipidemias and their relationship to morbidity and mortality

Dyslipidemias are prevalent in kidney transplant recipients. Among numerous reports monitoring lipid levels after transplantation, two representative studies reported high levels of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) in kidney transplant recipients (Figure 4).[13,50,51] Cardiovascular disease mortality is increased for transplant recipients compared to the general population

Figure 4

Prevalence of Dyslipidemias in Renal Transplant Recipients Receiving Immunosuppressive Therapy[13,50,51]



TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

(Figure 2), and several observational studies in kidney transplantation have reported a positive relationship between dyslipidemias and cardiovascular disease.[13]

A number of studies have shown correlations between lipid levels and subsequent chronic allograft nephropathy, graft loss, and decreased patient survival. In particular, a large analysis from Europe evaluated the effects of serum cholesterol as a continuous variable on long-term outcomes in renal transplantation. In this retrospective study of 676 recipients receiving primarily azathioprine- or cyclosporine-based immunosuppression and corticosteroids, serum cholesterol levels at 1 year posttransplantation proved an independent predictor of graft failure (death-censored RR, 1.33; 95% CI, 1.15-1.55; *P*=.0001) and patient survival (RR, 1.5; 95% CI, 1.1- 2.1; *P*=.01).[52] Furthermore, an analysis of 706 renal transplant recipients in the United States revealed that serum triglyceride levels were a risk factor for chronic rejection independent of acute rejection episodes (RR, 1.09; 95% CI, 1.03-1.16 for each 100 mg/dL; *P*=.034).[53]

Factors associated with posttransplant dyslipidemias

Transplant recipients have many of the same risk factors for dyslipidemias as does the general population, such as obesity, diet, genetic disposition, and insulin resistance. However, nontraditional risk factors, immunosuppressive drugs in particular, may also adversely affect the relationship between lipid levels and cardiovascular disease. Risk factors assessed in the FHS[6] and the Multiple Risk Factor Intervention Trial[54] reported an increased risk of death from coronary heart disease with increasing cholesterol levels in the general population, largely because of the negative impact of higher levels of LDL-C. Subsequent trials and a meta-analysis found that reducing total cholesterol and LDL-C levels also reduced coronary events and mortality in the general population and that the reduction in cardiac events and mortality was proportional to the extent of LDL-C reduction.[55] Risk factors for ischemic heart disease, identified by the FHS, were compared in a single-center study (N=1124) to posttransplant (>1 year) risk factors. A similar relationship between abnormal cholesterol levels and risk for ischemic events for both male and female transplant recipients was found. Even total cholesterol levels of 200 to 239 mg/dL seemed related to increased incidence of transplant ischemic heart disease.[5]

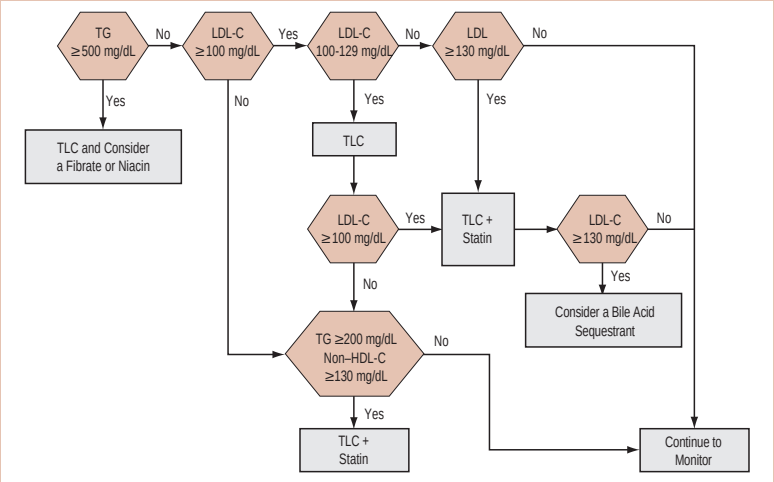
Management of dyslipidemias

The National Kidney Foundation K/DOQI guidelines place transplant recipients in the highest risk category (per the NCEP Adult Treatment Panel III), along with patients with chronic kidney disease. Accordingly, intervention is recommended when LDL-C levels are 100 mg/dL or higher. The prevailing opinion in the transplant community is that any transplant recipient with elevated LDL-C concentrations should be managed with both drugs and diet. Those patients with exceptionally high triglyceride levels require a slightly different approach (Figure 5).[13]

Few clinical trials have focused on therapeutic lifestyle changes (TLC) for kidney transplant recipients; however, studies in the general population suggest that exercise and weight reduction produce small improvements in cholesterol levels. Consultation with a renal dietician is important to ensure good nutrition, with emphasis on low-fat foods, soluble fiber, and use of plant sterols for fat replacement strategies. Alcohol in moderation should be discussed, but smoking cessation should be actively pursued.[13] For patients with modest elevations in total cholesterol values (eg, LDL-C 100-129 mg/dL), TLC can be tried for approximately 3 months before adding a lipid-lowering drug. If LDL-C levels are 130 mg/dL or greater, consideration should be given to starting a lipid-lowering agent along with TLC. For most patients, the agent of choice is a statin. However, the statin dose should be reduced in patients treated with cyclosporine. The goal of therapy should be LDL-C levels less than 100 mg/dL. However, if the LDL-C levels remain 130 mg/dL or greater, consider adding a second agent to the statin (eg, a bile acid sequestrant[13] or

Figure 5

National Kidney Foundation Treatment Guidelines for Adult Renal Transplant Recipients With Dyslipidemias[13]



TG = triglycerides; TLC = therapeutic lifestyle changes; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

Adapted with permission from K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. *Am J Kidney Dis*. 2003;41:S1-S91.

ezetimibe). In a preliminary study of 40 stable kidney transplant recipients, ezetimibe treatment did lower LDL-C levels[56]; however, ezetimibe use with cyclosporine is not recommended for cardiac transplant recipients because of a pharmacokinetic interaction that leads to a 12-fold increase in ezetimibe levels.[57,58] For some patients who continue to have high LDL-C levels despite therapy, especially if the risk for ischemic heart disease appears to outweigh the risk of acute rejection, consideration may be given to changing immunosuppression.

The role of immunosuppressive drugs in dyslipidemias

Corticosteroids, cyclosporine, and sirolimus can each contribute to dyslipidemias after kidney transplantation. However, these and other immunosuppressive agents can also adversely affect other cardiovascular disease risk factors (Table 1, page 3). Of course, the risk for rejection and graft dysfunction or failure must also be considered in selecting immunosuppressive agents. In the end, the clinician is left with a delicate balancing act of choosing between different risks and benefits from various immunosuppressive drug combinations.

Corticosteroids

Corticosteroids have long been associated with increased lipid levels, making immunosuppressive medication protocols that minimize the use of prednisone attractive. In a multicenter, randomized 6-month study of controlled corticosteroid dose reduction in kidney transplant recipients also receiving MMF and cyclosporine, a significant reduction in total cholesterol levels was observed in the group who had a 50% corticosteroid dose reduction then cessation (low/stop group, dose of 0-5 mg/day) compared to the control group (dose of 10 mg/day) who continued to receive corticosteroids (Figure 6). Systolic BP was also lower in the low/stop group, and there was a reduction in other corticosteroid-related side effects, such as bone loss. Although at 6 months, the low/stop group experienced a significantly higher rate of acute rejection than did the control group (23% vs 14%, respectively; *P*=.008), the rejections were mostly Banff grade I.[59]

In another multicenter study from Europe, investigators compared lipid levels at 3 and 6 months posttransplantation in a tacrolimus-based regimen that withdrew corticosteroids or MMF after 3 months. Immunologically low-risk patients were followed for an additional 3 months. Reductions in mean total cholesterol and LDL-C levels were significantly greater in the corticosteroid-withdrawal group (MMF + tacrolimus) than in either the control (corticosteroids + MMF + tacrolimus) or the MMF-withdrawal (corticosteroids + tacrolimus) group (*P*<.001). However, the changes in mean HDL-C levels resulted in little final change in the LDL-C/HDL-C ratio in the three groups between 4 and 6 months.[32]

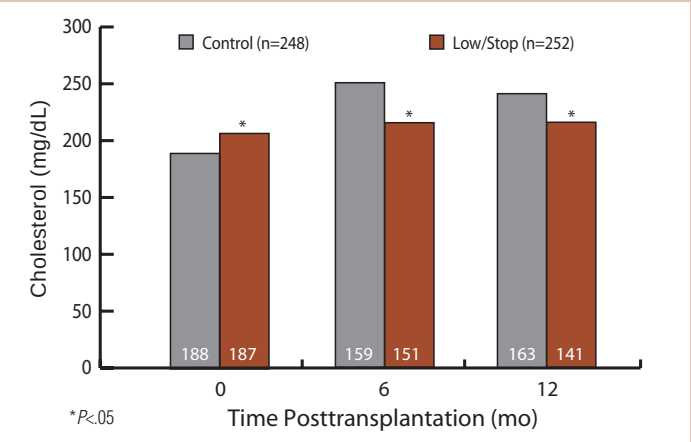
Calcineurin and target of rapamycin inhibitors

There is now substantial evidence that the CNI tacrolimus, unlike cyclosporine, does not affect lipid levels. This difference was demonstrated in a multicenter study in which stable kidney transplant recipients with established hyperlipidemia were randomized for conversion from cyclosporine-based immunosuppression to a tacrolimus-based regimen or continued treatment on the cyclosporine-based regimen. After 6 months of follow-up in patients converted to tacrolimus (n=27), total cholesterol levels decreased by 55 mg/dL (-16%, *P*=.003) and LDL-C levels decreased by 48 mg/dL (-25%, *P*=.001) compared to levels in recipients remaining on cyclosporine-based immunosuppression (n=26).[60] This finding has also been reported by other groups.[61-63] However, these results should be cautiously interpreted pending further understanding of the risk factors for cardiovascular disease in the transplant population.[64]

The target of rapamycin inhibitor sirolimus can cause elevations in lipoproteins that may be marked in some cases.[65] One randomized trial comparing sirolimus- and cyclosporine-based regimens reported that both groups showed significant increases in total cholesterol, HDL-C, and LDL-C levels by 1 month posttransplantation, compared with pretransplant levels (*P*=.001). Additionally, 64.5% of sirolimus-treated patients and 53.3% of cyclosporine-treated patients

Figure 6

Cholesterol Levels After Prednisone Withdrawal in Cyclosporine/Mycophenolate Mofetil-Treated Renal Transplant Recipients[59]



received lipid-lowering drug therapy within 1 year post-transplantation.[66] Another trial randomized recipients to tacrolimus-based immunosuppression (and corticosteroids) with either MMF or sirolimus for 6 months. Elevated concentrations of total cholesterol (*P*=.0001) and LDL-C (*P*=.001) were significantly more prevalent in the sirolimus-treated patients than in the MMF-treated group.[30] However, a number of positive effects of sirolimus, in particular on graft function, make its use a viable option for many patients.[67]

Role of lipid-lowering drugs

A substantial amount of data from randomized controlled trials in the general population indicates that statins are very effective in reducing levels of total cholesterol and LDL-C, and cardiovascular disease events. However, there is some uncertainty about the pathogenesis of cardiovascular disease in transplant recipients, or in those patients with chronic kidney disease, and whether treatment with statins will have similar efficacy to that in the general population. Results from "Die deutsche Diabetes Dialyse Studie" (4D) trial in patients with diabetes and ESRD showed no significant difference in the composite endpoint of major adverse cardiac events (MACE) in patients receiving atorvastatin compared to placebo.[68,69] The Assessment of Lescol in Renal Transplantation randomized controlled trial investigated the effect of fluvastatin on cardiac outcomes in kidney transplant recipients. This adequately powered study followed 2102 clinically stable transplant recipients (with total cholesterol levels between 155 mg/dL and 348 mg/dL) receiving fluvastatin (40 mg daily) or placebo for a mean follow-up of 5.1 years. Although fluvastatin lowered LDL-C levels by 32% and reduced the incidence of some cardiac events, the risk reduction for the primary endpoint of MACE was not significantly different from that in the placebo group (Table 4).[70] A further analysis failed to show that fluvastatin preserved graft function.[71,72]

Another critical outcome measure in kidney transplantation is the incidence of acute rejection. A number of studies investigated the possible effect of statin therapy on acute rejection. Only one study, with an unusually high rate of rejection in the control group, showed a significant improvement in acute rejection rates with statin therapy (*P*=.01),[73] whereas a number of recent studies have found no difference.[74,75] Thus, it does not appear that statins reduce the incidence of acute rejection in kidney transplant recipients.

The pharmacokinetic interaction between CNIs and statins, documented for cyclosporine and possibly tacrolimus, results in a higher blood level of the statin.[13,76] As a result, reduced doses of statins should probably be used in patients also treated with cyclosporine. Additionally, the fact that both statins and CNIs are metabolized by the CYP450 pathway can result in unwanted interactions with other drugs metabolized by the same pathway, such as CCBs and azole antifungals.[13]

In instances when treatment with diet and a statin does not achieve the goal of LDL-C levels less than 100 mg/dL, consideration should be given to adding a second agent. A bile acid sequestrant can be used effectively with a statin, but bile acid sequestrants are often not well tolerated.[13] The new cholesterol uptake inhibitor ezetimibe may be used in combination with a statin. Levels of ezetimibe may be increased in cyclosporine-treated patients, but the consequences of this are unknown.[56,57] Fibrates lower LDL-C levels in the general population, but increased blood levels of statins in patients also receiving cyclosporine and a statin make adding a fibrate to a statin in cyclosporine-treated patients risky.[13]

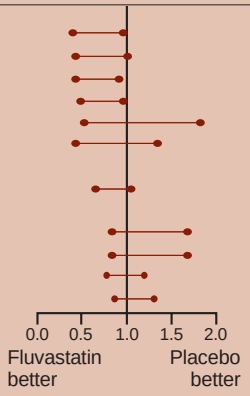
Conclusions

Cardiovascular disease is a prevalent, life-threatening issue for kidney transplant recipients. Neither hypertension nor dyslipidemias are well controlled. The immunosuppressive drugs critical for survival of the allograft cause both hypertension and dyslipidemias in kidney transplant recipients. TLC, together with BP- and lipid-lowering agents, are needed in the majority of transplant recipients. In the future, effective immunosuppressive agents that can replace corticosteroids and CNIs may help reduce cardiovascular disease risk.

Table 4

Endpoints in the ALERT Trial of Fluvastatin Therapy in Renal Transplant Recipients[70]

Endpoint	*P*	Risk Ratio (95% CI)
Cardiac death	.031	0.62 (0.40-0.96)
Definite nonfatal MI	.050	0.68 (0.40-1.00)
Cardiac death or definite nonfatal MI	.005	0.65 (0.48-0.88)
Cardiac death or definite or probable nonfatal MI	.032	0.72 (0.54-0.97)
CABG	.932	1.03 (0.58-1.81)
PCI	.357	0.80 (0.49-1.30)
Cardiac death or definite or probable nonfatal MI, CABG/PCI (MACE)	.139	0.83 (0.64-1.06)
Fatal or nonfatal cerebrovascular events*	.391	1.16 (0.83-1.63)
Noncardiovascular deaths	.288	1.20 (0.86-1.67)
All-cause death	.848	1.02 (0.81-1.30)
Graft loss or doubling of serum creatinine	.369	1.10 (0.89-1.36)



ALERT = Assessment of Lescol in Renal Transplantation; CI = confidence interval; MI = myocardial infarction; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; MACE = major adverse coronary events. *Fatal or nonfatal stroke, transient ischemic attack, reversible ischemic neurologic deficit, subarachnoid hemorrhage. Adapted with permission from Holdaas H, et al. *Lancet.* 2003;361:2024-2031.

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Impact and Management of Cardiovascular Risks After Kidney Transplantation

CME/CE Posttest and Evaluation

Release Date: June 2005 Expiration Date: June 30, 2006

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POSTTEST

Rebecca L. is a 35-year-old kidney transplant recipient (height, 5 foot 4 in., weighs 182 lb.) who has been engaged for 4 months. In part because of the sedentary nature and long work hours of her job as an auditor, she has gained 25 lbs in the 2.5 years since receiving her transplant. She has begun smoking again to try to curb her appetite. Rebecca lost her native kidneys from idiopathic nephrotic syndrome and was fortunate to have a cousin donate a well-matched kidney for transplantation. Rebecca talked to her nephrologist during a scheduled check-up about approaches to help her lose weight before her wedding. Her posttransplant clinical course included one episode of mild acute rejection (Banff I) within 3 months posttransplantation, which was resolved with pulse methylprednisone, and she has otherwise had an uneventful history beyond weight gain. Rebecca is currently on a maintenance immunosuppressive regimen of cyclosporine 3 to 3.5 mg/day (adjusted to through whole blood levels of 150 to 200 ng/mL), mycophenolate mofetil (1 mg bid), and prednisone (7.5 mg/day). Blood tests taken at her recent appointment revealed that her total cholesterol (from 200 to 230 mg/dL), low-density lipoprotein cholesterol (from 100 to 130 mg/dL), and triglyceride (from 160 to 180 mg/dL) levels have gradually increased over the last 12 months. Blood pressure is under control (130/76 mm Hg) with an angiotensin-converting enzyme (ACE) inhibitor. Renal function remains good.

1. Which nonimmunosuppression-related factors should be discussed with Rebecca?
   a. Nutrition counseling
   b. Smoking cessation
   c. Increasing exercise
   d. All of the above
   e. a and b

2. If cholesterol levels are not reduced by therapeutic lifestyle counseling, what would be your next approach?
   a. Add statin therapy
   b. Add fibrate therapy
   c. Withdraw mycophenolate mofetil
   d. Minimize corticosteroids
   e. Switch from the ACE inhibitor to a calcium channel blocker

3. Since Rebecca's lipid profile deteriorated during the last 12 months, would you modify her immunosuppressive protocol?
   a. Yes, eliminate cyclosporine
   b. Yes, eliminate sirolimus
   c. Yes, decrease cyclosporine doses
   d. Yes, decrease sirolimus doses
   e. Would not change immunosuppressive protocol

4. Renal transplant recipients have:
   a. A cardiovascular mortality rate of approximately 40%
   b. An overall higher cardiovascular mortality rate than the general population
   c. A nontraditional risk factor for cardiovascular disease related to some immunosuppressive drugs
   d. None of the above
   e. All of the above

5. Hypertension in renal transplant recipients:
   a. Is an independent risk factor for poorer long-term kidney graft survival
   b. Is frequently underdetected through routine clinic visit measurements of blood pressure compared to ambulatory blood pressure monitoring
   c. Can exhibit blood pressure changes with a diurnal variation similar to that in patients with chronic kidney disease
   d. None of the above
   e. All of the above

6. Use of calcineurin inhibitors (CNIs) in renal transplantation resulted in:
   a. Continued CNI maintenance therapy in all patients without drug minimization opportunities
   b. No changes in blood pressure compared to pretransplant values
   c. Studies showing that tacrolimus induced significantly more hypertension than did cyclosporine
   d. None of the above
   e. All of the above

7. Target blood pressure for kidney transplant recipients recommended in the National Kidney Foundation guidelines is:
   a. <145/90 mm Hg
   b. <140/85 mm Hg
   c. <140/80 mm Hg
   d. <135/85 mm Hg
   e. <130/80 mm Hg

8. In renal transplant recipients:
   a. Studies have shown little benefit for calcium channel blockers in comparison to diuretics, angiotensin-converting enzyme (ACE) inhibitors, or angiotension II receptor blockers for antihypertensive therapy
   b. ACE inhibitor use can reduce proteinuria
   c. Diuretics should not be used in cases of volume overload and sodium retention
   d. ACE inhibitors increase hematocrit or hemoglobin levels in those patients with posttransplant erythrocytosis
   e. Only 5% of patients will need to use more than one antihypertensive drug to manage blood pressure

9. Cholesterol levels were reduced by minimizing or eliminating the following drug(s) in immunosuppressive regimens after kidney transplantation:
   a. Cyclosporine
   b. Corticosteroids
   c. Sirolimus
   d. None of the above
   e. All of the above

10. Use of lipid-lowering therapies, immunosuppressive drugs, and other commonly used drugs must be approached carefully as undesirable pharmacokinetic interactions are known to occur between:
    a. Cyclosporine and high-dose statins
    b. Fibrates and statins and cyclosporine
    c. Statins and cyclosporine and azole antifungals
    d. All of the above
    e. None of the above

State-of-the-Art Management of Posttransplant Sequelae

Impact and Management of Cardiovascular Risks After Kidney Transplantation

CME/CE Posttest and Evaluation

Release Date: June 2005 Expiration Date: June 30, 2006

Posttest Answer Key (questions from page 9)

1. a b c d e	3. a b c d e	5. a b c d e	7. a b c d e	9. a b c d e
2. a b c d e	4. a b c d e	6. a b c d e	8. a b c d e	10. a b c d e

PROGRAM EVALUATION

The University of Minnesota would appreciate your comments regarding the quality of the information presented.

1. Each of the following program's educational objectives were fully met:
   - Recognize the prevalence and long-term impact of overall cardiovascular disease, and specifically hypertension and dyslipidemias, in renal transplant recipients
     ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree
   - Describe the risk factors for hypertension and dyslipidemias
     ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree
   - Identify the effects of immunosuppressive drugs on the development of hypertension and dyslipidemias
     ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree
   - Outline the modifications to immunosuppressive regimens to help manage hypertension and dyslipidemias
     ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree
   - Discuss the interventions to treat hypertension and dyslipidemias
     ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree
2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.
   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree
3. The educational activity has enhanced my professional effectiveness and improved my ability to treat/manage patients.
   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree ❑ N/A
4. The educational activity has improved my ability to communicate with patients.
   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree ❑ N/A
5. The information presented was free of promotional or commercial bias. ❑ Agree ❑ Disagree
6. What changes will you make in your practice as a result of participating in this program?

   _____

   _____
7. Comments/suggestions regarding *this* material:_____

   _____
8. Recommendations for *future* presentations:_____

   _____
9. What is the most important barrier to the optimal posttransplant management of patients receiving renal transplants? (select one answer)
   ❑ Patient adherence ❑ Infections
   ❑ Side effects of immunosuppressive agents ❑ Neoplasia
   ❑ Renal function ❑ Other
10. Approximately how many patients do you see per week?_____

    _____
11. Approximately what percentage of your patients are renal transplant recipients?

    _____

    _____

Full Name

Company/Affiliation

Street Address

City State ZIP Code

Email Address Fax Number

Degree: ❑ MD ❑ RN ❑ Other
❑ DO ❑ PharmD _____

Job Title
- ❑ Transplant Surgeon
- ❑ Nephrologist
- ❑ Transplant Coordinator
- ❑ Transplant Pharmacist
- ❑ Transplant Case Manager
- ❑ Nurse
- ❑ Other _____

Practice Type
- ❑ Private
- ❑ Group
- ❑ Transplant Center
- ❑ Academic

Practice Location
- ❑ Urban
- ❑ Suburban
- ❑ Rural

I certify that I completed this CME/CE activity. The actual amount of time I spent in this activity was: _____hours _____minutes.

Signature Date Completed

PHYSICIANS: Are you licensed in the United States? ❑ YES ❑ NO NURSES: State of license and number _____

All correspondence concerning the contents of this publication should be directed to:

SynerMed® Communications
Dept. WA48D
405 Trimmer Road
PO Box 458
Califon, NJ 07830

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